Feasibility of polymer-drug conjugates for non-cancer applications

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Abstract:
Polymer-drug conjugates have been intensely studied in the context of improving cancer chemotherapy and yet the only polymer-drug conjugate on the market (Movantik®) has a different therapeutic application (relieving opioid-induced constipation). In parallel, a number of studies have recently been published proposing the use of this approach for treating diseases other than cancer. In this commentary, we analyse the many and very diverse applications that have been proposed for polymer-drug conjugates (ranging from inflammation, to cardiovascular diseases) and the rationales underpinning them. We also highlight key design features to be considered when applying polymer-drug conjugates to these new therapeutic areas.

Keywords: non-cancer disease, polymer-drug conjugate, macromolecular prodrug, EPR effect, targeted drug deliver, inflammation, cardiovascular diseases.

List of abbreviations: AHPP: 4-amino-6-hydroxypyrazolo[3,4-D]pyrimidine; Apaf-1: Apoptotic protease activating factor 1; AsnPhePhe: Asparagine-phenylalanine-phenylalanine; $_{D}$-$(Asp)_{8}$: $_{D}$-Aspartic acid peptide; D: Degradable (E: Enzymatic degradation; H: Hydrolytic degradation); EDTA: Ethylenediaminetetraacetic acid; G: Generation; GFAL: Glycine-phenylalanine-alanine-leucine; GFGG: Glycine-phenylalanine-glycine-glycine; GFLG: Glycine-phenylalanine-leucine-glycine; GG: Glycine-glycine; 4G Glycine-glycine-glycine-glycine; GGPNle: Glycine-glycine-proline-norleuicne; GL: Glycine-leucine; HEMA: 2-hydroxyethyl methacrylate; HPMA: *N*-(2-hydroxypropyl)methacrylamide; I/R: ischemia reperfusion; Lact2G: Lactic acid-glycine-glycine; Lact4G: Lactic acid-glycine-glycine-glycine-glycine; LMHC; low molecular weight hydroxyethyl chitosan; N/A: Not applicable/Not stated; OR: Oxidation responsive; PAA: Poly(acrylic acid); PAHA: Poly[α,β-(*N*-2-hydroxyethyl-DL-aspartamide)]-poly[α,β-(*N*-2-aminoethyl-DL-aspartamide)]; PAMAM: Poly(amidoamine); PCL: Polycaprolactone; pDMAEMA: Poly(dimethylamino)ethyl methacrylate; PEG: Poly ethylene glycol; mPEG: methoxy PEG; sPEG: star PEG; PGA: Polyglutamic acid; PHEA: α,β-poly [(*N*-2-hydroxyethyl)-DL-aspartamide]; PHPA: Poly[α,β- (*N*-3-hydroxypropyl-DL-aspartamide)]; PHPMA: Poly *N*-(2 hydroxypropyl)methacrylamide; PMAA: Poly(methacrylic acid); PVP: Poly(vinylpyrrolidinone); SMA: Styrene-maleic acid.

1. Introduction

Pioneering work on polymer-drug conjugates (PDC)s started in the 1950s [1*], but it was only in 1975 that the concept of PDC as a means of achieving drug targeting was formalised by Ringsdorf [2**]. Since then, research in this field has traditionally focussed on their applications in cancer to enhance the delivery of chemotherapeutic agents to tumour tissues. Interestingly, whilst a number of conjugates progressed to clinical trials with some reaching Phase 3 [3**,4], the only polymer-drug conjugate on the market (PEG-naloxone, naloxegol, Movantik®) is actually used for a different therapeutic application (to treat opioid-induced constipation) [5]. PEG-naloxone is a conjugate in which a PEG oligomer (7 units, MW of <1 kDa) and drug molecules (naloxone) are covalently attached *via* a linker [6]. However, the rationale for this system (and its subsequent application) is fundamentally different from that of traditional polymer-drug conjugates (see Fig. 1). For example, in traditional polymer-drug conjugates the purpose of the polymer is to increase selective accumulation in the tumour

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through passive accumulating in the tumour tissue, by the enhanced permeability and retention effect (EPR) [7**,8]. In Movantik®, however, the PEG is incorporated to prevent naloxone from penetrating through the blood-brain barrier, hence maximising its peripheral effects [5].

Whilst many reviews focus on the use of polymer-drug conjugates for cancer, the application of polymer-drug conjugates for non-cancer diseases has been less widely reviewed [9**,10]. This review therefore critically appraises the application of PDCs in diseases other than cancers, with a focus on the rationales and the key considerations that have underpinned their design (Tables 1 and 2), with information summarised according to the therapeutic area. We finish the commentary with some general considerations about this emerging field.

2. Polymer-drug conjugates in diseases other than cancer

The strategy of conjugating low molecular weight drugs to polymeric carriers has been applied in order to develop novel therapeutic systems towards diseases other than cancer. These applications include infections, inflammation, nervous system diseases, cardiovascular disease, endocrine disease, digestive diseases, bone problems, eye diseases, and wound-related problems as summarised in Table 2. In these cases, PDCs have generally been developed in order to overcome limitations associated with therapeutically active drugs that are typically used in these diseases, for example poor solubility, undesirable pharmacokinetic properties, or low bioavailability at the disease site.

2.1. Polymer-drug conjugates as polymer therapeutics for infections

2.1.1. Antibiotics:

PDCs of different antibacterial agents have been developed in order to enhance their therapeutic activity against different types of bacteria, as summarised in Table 2. Three main aims were explored in these studies, specifically: a) to provide a sustained release of the drug which led to a reduced toxicity, b) to selectively target the drug to the desired site of action, c) to extend the $t_{1/2}$ of the drug. The first studies in this area were reported in the 1960s where water-soluble polymeric derivatives of various penicillin antibiotics using polyvinylpyrrolidone were developed [25–27]. Later, in a study reported in 1989, the aim was to reduce toxicity associated with the administration of isoniazid against *Mycobacterium tuberculosis* by developing a system for the sustained release of isoniazid. Isoniazid was linked *via* an amide bond to poly-α,β aspartic acid [12] and to poly($_{DL}$-succinimide) [13]. The poly($_{DL}$-succinimide)-isoniazid conjugate exhibited delayed release of the isoniazid in the simulated gastric environment pH (1.2) due to the gradual degradation of the amide linkage *in vitro* [13]. A similar approach was used also for Peptoid 7, a small molecule with an ability to neutralise lipopolysaccharides and potentially treat septicaemia, to provide a controlled release of this drug and again to improve its safety profile [15]. Peptoid 7 was linked to PGA and PEG *via* different spacers: the dipeptide GG with or without lactic acid (Lact) through amide and ester bonds, respectively. *In vitro* release studies indicated that the conjugates were stable plasma, but released the drug after exposure to cathepsin B.

The second rationale for employing conjugation was to enhance the targeting of antibiotics to specific cells and tissues depending on different mechanisms. Azithromycin was linked *via* an ester bond to a PAMAM G4 dendrimers to increase the delivery of azithromycin and to improve its antibacterial activity against *Chlamydia trachomatis* [21]. The design of the conjugate was based on the ability of dendrimers to accumulate in inflamed tissues (such as chlamydial arthritis) due to the leaky vasculature of the area. This allows accumulation of

macromolecules which is enhanced further as a result of the dendrimer's affinity for glucosaminoglycan released in the inflamed tissues [28–31]. *In vitro* studies indicated high uptake of the fluorescently-labelled azithromycin dendrimers by the *Chlamidya trachomatis* infected human epithelial type 2 (HEp-2) cells in both acute and persistent states of infection with high localisation of the dendrimers in the inclusions.
In other studies, selective accumulation at the infected site was achieved by using targeting moiety rather than exploiting the natural accumulation of the systems in the tissues. As mannose receptors are expressed on the surface of the macrophages [32], conjugates of norfloxacin were grafted with mannose moieties to increase accumulation in macrophages infected by *Mycobacterium tuberculosis* bacilli. The effectiveness of the strategy was the proven *in vivo* (*M.Bovis* BCG infected mice), where, unlike the non-mannosylated conjugate, the mannosylated conjugate was effective against isoniazid-insensitive mycobacteria in the liver, spleen, and lung [17,18]. Other targeting ligands have been suggested such as a carboxymethylation of glucan to target T.B infected macrophages [19]. One particularly interesting example of actively targeted conjugate is PAMAM (G3)-LED209 for Gram negative bacterial infection. In this case, LED209 had a dual role as an active drugs and as a targeting ligand [20]. The mechanism of action of LED209 is based on the allosteric alteration of lysine residues of QesC which, consequently, impairs the function of QesC and significantly reduces the virulence of the pathogens. QesC is a histidine sensor kinase that is found in at least 21 Gram negative bacteria that induce infection in humans and also plays an important role in activating the expression of the virulence genes in these pathogens. Moreover, LED209 does not display toxicity and does not influence the bacterial growth [33]. *In vitro* analysis demonstrated greater accumulation of the LED209-dendrimers in the *bacteria* cells than in mammalian SW480 cells. Furthermore, G3 PAMAM-LED209 significantly inhibited the expression of virulence genes in *EHEC* and *S. typhimurium,* and displayed potent antibacterial activity against susceptible and resistant Gram negative bacteria.

The third rationale for applying a PDC strategy for antibacterial usage was to address unfavourable pharmacokinetic properties of certain antibiotics. For instance, vancomycin is a glycopeptide antibiotic that requires infusion every 6 hours to obtain effective therapeutic levels due to renal elimination ($t_{1/2}$ of 4.8 h) [34]. PEG-vancomycin conjugates were prepared to increase the mean residence time of the drug in the blood stream by reducing the renal excretion with a size exclusion mechanism [23]. All conjugates showed antibacterial activity against *S. aureus* in infected mice. Furthermore, all conjugates exhibited high AUC with a range of 171-2184 h.μg/mL in comparison with native vancomycin (78.8 h.μg/mL), which indicated that the conjugate might require less frequent administration than the free drug.

2.1.2. Antifungal

The rationales behind the application of a conjugation strategy within the context of treating fungal infections are mainly to reduce the toxicity of the drug by increasing water solubility, and/or to enhance the selective drug targeting to the fungal infected tissues and increase drug accumulation (which is based on the specific environmental pH of the infected tissues and on a fungi specific enzyme which mediates release of the drug, Table 2). Amphotericin B and nystatin are antifungal drugs [44] whose applications are limited by poor water solubility and other unfavourable characteristics (high nephrotoxicity for amphotericin B; low gastrointestinal absorbance and toxicity for nystatin).

In order to improve water solubility, it was important to select highly hydrophilic polymeric carriers, and, indeed, a natural polysaccharide (arabinogalactan) was used for this purpose in most studies that aimed to improve water solubility [35,37,39]. The remaining

studies used another common water-soluble polymer (PEG) [36,38]. The solubility of amphotericin B was highly improved after polymer conjugation (200 - 2000 folds increase for arabinogalactan conjugates and 140-250 folds for PEG conjugates). An increase in solubility is particularly important for amphotericin B because its physical characteristics, in particular its tendency to self-assemble, have been associated with nephrotoxicity [45]. Indeed, systems, such as liposomal formulations of this drug, are significantly less toxic than the native one (eg. AmBisome® is about 50 times less toxic *in vivo* than Fungizone® [46,47]). Similarly, conjugation to a polymer, and subsequent increase in water solubility also led to a decrease in the toxicity of amphotericin B [48]. The decrease in toxicity depended on the linker, which presumably correlates with the rate of drug release rate. For instance, when amphotericin B was conjugated to arabinogalactan through an amine or imine linkage [35,37], the latter was the least toxic and did not cause any measurable damage to the kidney *in vivo*.

The second rationale for using PDCs with antifungals was to improve targeting of fungal infected tissues. The targeting strategy relied on selective drug release, promoted by either the acidic pH of the infected tissues, or by the presence of a specific hydrolytic β-glycosidase enzyme which is found in pathogenic fungi but not human tissues [49]. For these purposes, amphotericin B was linked to PEG *via* a pH labile linker (typically an imine linker) [41]. The conjugates were relatively stable when challenged in human physiological fluids (blood, serum, or/and plasma) with a $t_{1/2}$ of 2-5 h, while at pH 5.5 the $t_{1/2}$ was 2 min. The enzymatic targeting strategy was employed using β-glycosidase labile linkers. Conjugates of amphotericin B and of nystatin were synthesised containing this type of linkers. The strategy proved successful as both conjugates were stable in phosphate buffer at pH 7.4 *in vitro,* while drug release was observed in the presence of the enzyme [42,43*].

2.1.3. Antiviral

The concept of macromolecular prodrugs has been widely applied to improve the therapeutic effects of several antiviral drugs by focusing on: a) improving the water solubility and providing controlled drug release; b) prolonging the antiviral activity by extending the $t_{1/2}$; c) enhancing the selective drug targeting of the virally infected tissues; and d) reducing unwanted cellular interactions. Examples of these systems are presented in this section and are summarised in Table 2.

The conjugation to a hydrophilic carrier was employed to improve the therapeutic activity of acyclovir, an antiviral agent used against herpes simplex type I/II, by improving its water solubility and offering controlled release [57]. In this study, β-cyclodextrin was used for conjugating acyclovir through an ester bond. The solubility of acyclovir was increased two-fold after the conjugation. *In vitro* hydrolysis studies at different pHs and in the presence or absence of esterase showed that drug release was affected by the conditions (100% drug release in presence of esterases). Similarly, a PDC strategy was applied to another reverse transcriptase inhibitor – stavudine – in order to achieve a delayed drug release and reduce its metabolism, and consequently, prolong its $t_{1/2}$. Chitosan was covalently linked to stavudine [54,55] and the conjugate was used to prepare nanoparticles. *In vitro* release studies of both the conjugate and nanoparticles revealed that prolonged release of the drug was provided by both systems. This prolonged release profile enhanced the anti HIV activity by enabling the stavudine to bypass the rate limiting step of metabolic monophosphorylation. Interestingly, the conjugate was 13 times less toxic than the free drug, which could suggest, in addition to extending drug release, that the conjugate masked the toxicity of the drug.

Polymeric systems were also developed to enhance the $t_{1/2}$ of zidovudine, a reverse transcriptase inhibitor used for HIV treatment, by providing a sustained release of the drug

and decreasing its renal elimination depending on the MW of the polymers [50,56,58,61,62,69,70]. Dextrin (MW 6600 g/mol) was used for the conjugation with zidovudine for this purpose [62]. *In vivo* studies showed that the strategy worked in that conjugation increased the $t_{1/2}$ of zidovudine after i.v administration from 1.3 to 19.3 h due to the effect of dextrin's high MW on the renal filtration. It is important to mention that, in addition to extend the $t_{1/2}$, some polymers were used also to produce a synergistic antiviral effect with zidovudine. Thus sulfated laminaripentaose and κ-carrageenan conjugates of zidovudine showed enhance antiviral activity compared to the free drug [56,70].
Selective targeting of virally infected tissues is another reason for which developing PDCs of antivirals has been suggested. In this context, most studies reported the use of a targeting moiety to promote receptor-mediated internalisation of the antiviral agent. Examples include the use of biotin and R.I.CK-Tat 9 (a peptide which contains D-aminoacids in the inverse order of the natural L-peptide, thus ensuring better stability) for HIV [63,64]; lactobionic acid for HBV; [65]; and lactosamine for HCV [66]. For example, lamivudine, an anti-hepatitis B agent, was conjugated to chitosan grafted with lactobionic acid which can enhance hepatic targeting [65]. Interestingly, the presence of lactobionic acid enhanced the hepatic targeting and cellular uptake of lamivudine. Furthermore, the addition of lactobionic acid resulted in improved solubility and reduction in toxicity. A similar concept was employed for saquinavir which was the first approved FDA HIV-1 protease inhibitor [75]. A library of saquinavir polymeric conjugates based on PEG was prepared using biotin or R.I.CK-Tat 9 as a targeting ligand. The design of these systems allowed the use of the targeting ability of biotin and R.I.CK-Tat 9 and their anti HIV activity.[63,64]. *In vitro* studies indicated that the addition of biotin to the conjugates increased their antiviral activity, and a further increase in the activity was noticed upon replacing biotin with R.I.CK-Tat 9 (a peptide with cell penetrating properties [76]). Importantly, the anti-HIV-1 activity of PEG-R.I.CK-Tat 9- saquinavir conjugate was similar to that of saquinavir, and the cytotoxicity of the conjugate was lower than that of saquinavir against non-infected MT-2 cells.

The macromolecular prodrug strategy was also used to improve the therapeutic applications of ribavirin by reducing its administration-associated toxicity. Ribavirin is a broad-spectrum antiviral used particularly in hepatitis C. However, it exhibits a dose dependent-toxicity due to its accumulation in red blood cells [77]. To improve the toxicity profile of ribavirin, a conjugate with poly(acrylic acid) was developed that incorporated an ester linkage [71*]. *In vitro* studies indicated that conjugation reduced the ability of the ribavirin to accumulate in red blood cells, which, in turn, led to a significant decrease in its toxicity.

2.1.4. Antiprotozoal agents

Leishmaniosis and malaria are parasitic diseases that are induced by the intracellular protozoans of the genus Leishmaniosis and *Plasmodium* parasites and transmitted by *Anopheles* mosquitoes [86,87]. Interestingly, in the case of leishmaniosis, the idea of applying PDCs within this concept was based on the similarity observed between the parasite organelles and human lysososomes, which share the same acidic pH and proteolytic enzymes such as cathepsins B, D, and H [83]. PDC had been proven to be able to target human lysosomes in their applications for cancer [88],Therefore, it was hypothesised that PDCs could improve the targeting of the drug to the parasite infected cells (Table 2).

Amphotericin B has already been discussed in section 2.1.2 (antifungals), however, this drug is also an effective antileishmanial agent [89]. Conjugation of amphotericin B to polymers has therefore also been explored to target amphotericin B to the location of parasites in the host macrophages. There was also scope for active targeting as the

leishmanial parasites have cell surface glycoproteins that mainly contain mannose residues [90], which enhance their uptake by hepatic macrophages *via* mannose receptors [91]. Therefore, amphotericin B was conjugated to an (HPMA) copolymer *via* a cathepsin labile peptide linkage with or without mannosamine. The conjugates exhibited antileishmanial activity against intracellular *L. donovani* amastigotes in the tested host macrophages cells *in vitro*. Their activity was of the same magnitude as free amphotericin B as well as Fungizone®. *In vivo* studies in infected BALB/c mice indicated the ability of the pHPMA-GFLG-amphotericin B conjugate to inhibit the parasite burden in levels similar to that of the AmBisome®. However, there was no significant impact of linking mannosamine residues to the conjugate on its antileishmanial activity.

The conjugation concept was also used to prolong the therapeutic activity of drugs. Primaquine (a quinolone analogue) is an antimalarial agent that is effective against different types of malaria [92]. However, its clinical applications are limited by its rapid metabolism to carboxyprimaquine ($t_{1/2}$: 4-9 h), and toxicity [93]. To overcome these limitations, primaquine was covalently conjugated through a carbamate linkage to two types of polyaspartamide polymers (PHEA and PHPA). The conjugation reduced the metabolism of primaquine [80]. In *vivo* studies in mice demonstrated that PHEA and PHPA conjugates (administered orally) exhibited prolonged antimalarial activity (for +28 days) against *Plasmodium. berghei*.

The strategy of combination therapy using PDCs was employed to improve the therapeutic activity of both antimalarial agents primaquine and dihydroartemisinin (artemisinin analogue, a novel antimalarial agent [94]). They were covalently linked to polyphosphazene (a synthetic polymer), and nanoparticles of the conjugates were prepared to enhance the delivery of the drugs to the hepatic tissues. *In vivo* studies indicated that all formulations at low doses displayed antimalarial activity against *P. berghei* (NK 65) infected mice that was comparable to that of the free drugs, and the protection activity lasted without any recrudescence for more than 35 days [85].

2.2. Polymer-drug conjugates as polymer therapeutics for inflammation

The concept of conjugation has been widely applied within the context of inflammation and other related diseases (Table 2). This is a particularly interesting therapeutic application, because the rationale for using polymer-drug conjugates in inflammation stems from similarities in the pathophysiological features of the inflamed tissue (such as rheumatoid arthritis) and those of cancer. Specifically, the key features observed in inflamed tissues (increased blood supply to the area with oedema due to the leaky blood vessels [130,131]) are reminiscent of the hyperpermeability of tumour vasculature, due to the EPR effect [8,132]. For this purpose, a copolymer conjugate of dexamethasone and HPMA [133] was prepared containing a pH labile (MA-Gly-Gly-NHN= dexamethasone) monomer system to provide selective targeting and release of the drug at the site of inflammation based on the EPR-like effect and the acidic environment (pH 4.4- 5.6) induced by rheumatoid arthritis [134–136]. *In vitro* studies demonstrated that the release was pH dependent, where no release of the drug was detected at pH 7.4, and at pH 5 its release followed zero-order kinetics with 14% of the drug being released during the course of the study (14 days). Moreover, *in vivo* results demonstrated that the conjugate exhibited longer lasting and enhanced joint protection and anti-inflammatory effects compared to the free drug. The tropism of some polymeric systems towards some tissues or organs was also employed to achieve passive accumulation of the conjugated drugs. This was used to develop a PDC for an anti-inflammatory drug, *N*-acetyl cysteine (NAC), that shows promising therapeutic activity for neuro-inflammation but poor oral bioavailability associated with a short $t_{1/2}$. Therefore, it was conjugated to PAMAM (G 3.5) to improve its delivery to the activated microglial cells (the biological target cells of *N*-

acetyl cysteine). The system was based on the ability of PAMAM dendrimers to accumulate in these cells (see section 2.1.1), to provide a cytosolic delivery of the drug, and on the intracellular hydrolysis of the linker in the presence of glutathione (which is found in very low levels in plasma and in high levels inside the cells [137]). *In vitro* release studies indicated that in the presence of glutathione at its intracellular concentration, 45% of *N*-acetyl cysteine was released from PAMAM-$(COOH)_{46}$-$(NAC)_{18}$, while no release of NAC was detected in the absence or even at the blood levels of glutathione. In addition to that, PAMAM dendrimers exhibited rapid accumulation within the cells, and the conjugate showed improved anti-inflammatory activity compared to the free drug [121*]. The same idea was applied for erythromycin, an antibiotic with promising anti-inflammatory activity [22*]. Erythromycin has anti-inflammatory properties, with the ability to concentrate preferably in monocyte/macrophages exhibiting a 'phagocyte-targeted delivery' feature. Moreover, *in vitro* and *in vivo* studies indicated that erythromycin inhibited osteolysis and orthopaedic wear debris mediated inflammation [138]. However, the delivery of erythromycin to the periprosthetic inflammation site without displaying systemic side effects is a considerable obstacle. To overcome this problem, erythromycin was conjugated to PAMAM G4 *via* an ester linkage to provide a sustained drug release combined with selective targeting to the inflamed tissues. *In vitro* release studies showed that about 90% of the erythromycin was liberated within 10 h of incubation. Importantly, the conjugate was not toxic and significantly reduced the generation of NO_2^- in lipopolysaccharide stimulated RAW 264.7 cells compared to the free drug. Passive accumulation of polymeric carrier/macromolecular dextran in the spleen and liver [139] was used to provide selective targeting of immunosuppressive drugs to attenuate the acute rejection of liver transplantation in rat models [117*]. In this study, dextran was conjugated to methylprednisolone. *In vivo* studies indicated that after administering a single dose of the conjugate, the mean survival time of the treated animals was significantly increased (27.5 days) compared to 10.5 days in methylprednisolone-treated animals. A significant decrease in the levels of hepatic injury markers (bilirubin, ALP, ALT, and AST) was noticed in comparison to methylprednisolone treated or control animals. Moreover, conjugated methylprednisolone significantly reduced the rejection activity index, and the hepatic and plasma levels of TNF-α, compared to other groups. Another interesting feature present in the inflamed tissue (overproduction of ROS) was also elegantly exploited to produce selective drug release at the target site. For instance, an oxidation responsive copolymer of an acrylate derivative of naproxen (with a phenylboronic ester) was polymerized through the reversible addition-fragmentation chain transfer using a PEG chain transfer reagent, and nanoparticles were prepared from the conjugates. *In vitro* release studies showed almost no release of naproxen at pH 7.4, while >92% of the drug was released after oxidative activation of the conjugate by H_2O_2 (an ROS that is produced *in vivo*) [123].

Active targeting was also employed for the selective delivery of drugs to the site of inflammation in order to improve their efficacy and reduce their toxicities. This is based on the overexpression of folate receptors in inflammation activated macrophages [140]. Therefore, PAMAM G5 was conjugated to methotrexate (anti-inflammatory) and folic acid (FA) (as a targeting moiety). *In vitro* binding studies highlighted that the binding affinity of the G5-FA-methotrexate to different tested macrophages was dose and energy-dependent, and was blocked by the presence of free folic acid. *In vivo* studies in adjuvant-induced arthritic rats indicated that the conjugates exhibited similar preventive effects to free methotrexate at an equivalent dose. Moreover, the conjugate exhibited no spleen toxicity in comparison to the free drug [111].

Combination therapy was another rationale for using PDCs in treating inflammation related diseases. Methotrexate was covalently linked to hyaluronic acid (HA, an endogenous

polysaccharide) using GFLG and AsnPhePhe as lysosomal enzyme cleavable linkers [113]. In this study, the development of a system based on HA's ability to improve the viscoelasticity of synovial fluid (a lubricating effect) and on the overexpression of CD44 receptors on the surface of synovial cells (which mediate the endocytosis of HA). In addition, lysosomal targeted release of methotrexate was employed. *In vitro* studies indicated that methotrexate derivatives of GFLG and AsnPhePhe were hydrolysed in the presence of cathepsins B, D, and L, which suggested the intracellular release of methotrexate. However, a significant reduction in knee diameter (swelling) of rats with arthritis was observed only after intra-articular injection of the conjugate with AsnPhePhe.

The similarities between features observed in the inflamed tissues and in cancer (e.g. EPR-like effect, presence of specific enzymes or species, the acidic pH, and receptor expression) make this application, in our view, a particularly interesting and promising area for further study.

2.3. Polymer-drug conjugates as polymer therapeutics for diseases of the nervous system

Polymeric prodrugs have also been used to improve the therapeutic activity of drugs used for treating diseases of the nervous system (Table 2). The application of this concept aimed at protecting the drugs from the degradation and/or at providing targeted release of the drug at the intended site. Therefore, PDCs of $_{L}$-dopa and dopamine were developed to reduced their degradation [141,142,144]. A macromolecular prodrug of $_{L}$-dopa and PHEA was prepared to inhibit the peripheral oxidation of the drug, and to improve its water solubility[141].

The targeting release strategy using macromolecular systems was also applied to a new emerging field within neurodegeneration. Familial amyloid polyneuropathy (FAB) is a type of neurodegenerative amyloidotic disease that occurs mainly in the peripheral nervous system (PNS) due to a mutation in the transthyretin (TTR) protein which leads to its aggregation in the tissues, and formation of fibrils [147]. The tetracycline doxycycline, a neuroprotector, effectively decreased standard markers of fibril association and disrupted TTR fibril formation [148]. Therefore, a polymeric conjugate of doxycycline was developed to enhance the release of the drug at the targeted site as a result of the surrounding acidic environment (due to inflammation). The system consisted of PGA as a carrier and the conjugation was achieved using amide, ester, or amino acid linkers [143*]. *In vitro* studies revealed that the conjugates were stable in plasma for 24 h and none of them were haemolytic. Interestingly, the release of doxycycline was detected from PGA-doxycycline with an ester bond, while no doxycycline was released from the conjugate with an amide linkage after incubation for 16 days. Among the prepared conjugates, PGA-CONH-doxycycline was effective in decreasing fibril length and numbers of the most aggressive TTR mutations (TTR Leu55Pro). This effect might be due to the synergistic activity of the locally accumulated doxycycline and PGA negatively charged carboxyl groups which limit the intramolecular interaction of TTR β-sheet and induced the disruption of fibrils. It is important to highlight that the release of doxycycline was not essential for its activity. *In vivo* bio-distribution studies revealed the renal excretion of PGA-CONH-doxycycline with no specific organ accumulation/toxicity in mice with an early stage of FAB.

With regards to the CNS, an interesting application is the use of PDC, to prevent permeability across the BBB, and, consequently, stop unwanted central side effects. Movantik® was developed to prevent the permeation of naloxol, an opioid antagonist used for treating opioid induced constipation, through the BBB, and consequently, reduce its central side effect. In this case, naloxol is conjugated to a non-biodegradable PEG (low MW <1000

Da) through a non-biodegradable ether bond. This conjugation offered the peripheral targeting of opioid receptors after oral administration of the conjugate and prevented the permeation of naloxol through the BBB. Clinical studies indicated rapid absorption of the conjugate after oral administration (<2 h), with a $t_{1/2}$ of 6-11 h [145,149].

Finally, based on the same rationale, a recent study attempted to localise the effect of haloperidol (a D_2 receptor antagonist used as antipsychotic) on either side of the BBB, while retaining affinity for the receptor. The system contained haloperidol that was linked to PEG *via* a non-biodegradable carbamate linker [146*]. It was hypothesised that the size of the conjugate would inhibit the passive diffusion of haloperidol through the BBB and, consequently, would localise its effect on one side of the membrane. *In vitro* studies indicated high stability of the conjugate in rat plasma, (2% release of haloperidol in 1 week). Importantly, the conjugate retained affinity for D_2 receptors in membranes of CHO cells. *In silico* calculations showed the conjugate was very likely to be BBB impermeable.

In summary, the concept of conjugation is now considered as a new and promising approach to obtain optimal therapy for NS disorders. It allows the protection of the drug against degradation and its sustained release within the inflamed tissues. Importantly, it also enhances the peripheral targeting of specific receptors hence reducing unwanted side effects of the drugs by preventing their crossing through the BBB.

2.4. Polymer-drug conjugates as polymer therapeutics for cardiovascular diseases

Several macromolecular prodrugs have been developed for treating diseases associated with the cardiovascular system (CV) namely: hypertension, dyslipidaemia, ischemia and related problems (Table 2). These systems aim to improve the solubility of the free drug, by linking drugs to hydrophilic carriers, offering the benefit of combination therapy, and retaining the drugs at their sites of administration.

The concept of improving the water solubility of drugs by conjugation was used to enhance the poor water solubility of 4-amino-6-hydroxypyrazolo[3,4-d]pyrimidine (AHPP). This compound is a potent antihypertensive that inhibits xanthine oxidase, and consequently reduces the interaction of NO and superoxide O_2^- (found in elevated levels in patients diagnosed with hypertension [157]). However, the main obstacle for its clinical application is its poor water solubility. To overcome this limitation, a conjugate of AHPP was produced using the copolymer of styrene maleic acid (SMA, SMA-AHPP) [152]. *In vitro* studies indicated the high-water solubility of SMA-AHPP with a saturated concentration in distilled water (or physiological saline) of 22 mM, while the free HAPP was insoluble in either solution. Free drug release was higher at pH 5.5 (30% /day) than at pH 7.4 (22%/ day). Interestingly, oral administration of SMA-AHPP in spontaneously hypertensive rats resulted in an extended antihypertensive effect of the conjugate which lasted for at least for 7 days.

Combining the therapeutic activity of the polymer and the drug was another rationale to apply the concept of PDCs for CV diseases. Ischemia reperfusion (I/R) injuries are known to induce endothelial tissue damage by the overproduction of free radicals and reducing the levels of NO [158]. A macromolecular prodrug of PEG and butanediol mononitrate was developed to neutralize the oxidative stress and to normalize the response of blood vessels [155]. This system was designed to combine the ability of PEG to suppress the production of free radicals with the release of NO from butanediol mononitrate. A range of conjugates were prepared using β-glutamic acid as a spacer to produce polymers with dendritic structures and increased drug loading. *In vivo* studies in male Syrian hamsters with I/R injury indicated a significant increase in the flow and viscosity of red blood cells, and in the arteriole diameters after the treatment with PEG-butanediol mononitrate. This was accompanied by a significant

decrease in the permeability of capillaries and venules compared to controls. Moreover, PEG-butanediol mononitrate induced a significant reduction in the adhesion of leukocytes, in the plasma levels of vWF factor, and in lipid peroxidation compared with controls.

Achieving the localized effect of the drug in blood vessels was the rationale behind conjugating 17β-estradiol to dextran with Mw of 2 MDa [156*]. 17β-Estradiol is an estrogen with promising cardiac protective effects, however, its applications in this therapeutic area are limited by the uncontrolled stimulation of estrogen receptors in the body and the effect on coagulation [159]. Therefore, it was conjugated to a very large polymeric carrier to restrict the effect of 17β-estradiol in vascular lumens. *In vivo* bio-distribution studies revealed no diffusion of the conjugate into red blood cells, and no evidence of the accumulation of the conjugate in the heart, lung, or liver. A long residence time of the conjugate was also noticed, with slow renal excretion. Importantly, there was no significant effect of the conjugate on the rat's uterus. Moreover, the conjugate produced myocardial protection of 85% and reduced the damage of the myocardial tissue due to coronary ischemic reperfusion by half in gonadectomised male Wistar rats.

Effective treatment of CV diseases with minimised or even removed side effects might be achieved using macromolecular prodrugs. This concept offered the use of several effective drugs with limited applications. This could be obtained by localising drug effects at defected tissues or by improving their water solubility.

2.5. Polymer-drug conjugates as polymer therapeutics for endocrine diseases

In the context of endocrine diseases PDCs have been suggested for hormone replacement therapy and diabetes (Table 2). With regards of hormonal replacement therapy, the purpose was to improve the water solubility of estradiol, which was obtained by the same mechanism that was described in previous sections [160,161].

For diabetes, however, the purpose of using PDCs was to overcome limitation associated with a specific drug: phloridzin. This is a potent, experimental antidiabetic agent, which, however, is converted to a toxic metabolite (phloretin) by the hydrolytic effect of β-glycosidase in the intestine. Conjugation of phloridzin to a macromolecular carrier (γ-PGA or PAMAM) was achieved through a non-biodegradable bond. The test conjugate significantly inhibited intestinal glucose uptake *in vivo* after oral administration when compared to controls. This was likely due to the steric bulk of the polymer minimising hydrolysis of conjugated phloridzin by intestinal β-glycosidase enzymes and consequently, retaining its activity [162]. However, conjugation reduced the *in vitro* activity of phloridzin by ca. 90%. Moreover, even though the phloretin was entrapped within the backbone of the non-absorbable polymer, its latent toxicity remained a risk factor for patients who received the conjugate for a long time. Therefore, in another study, phloridzin and γ-PGA were replaced with arbutin (an experimental agent with antidiabetic activity) and PAMAM G3 [164*]. *In vitro* results indicated that the PAMAM-arbutin exhibited an inhibitory effect comparable to that of the PAMAM-phloridzin even though the effect of free arbutin was 30 time lower than that of free phloridzin. Moreover, *in vivo* studies indicated the ability of PAMAM-arbutin to inhibit uptake of $_{D}$-glucose despite the free arbutin showing no influence on the induced hyperglycaemic effect.

These applications of PDCs to diabetes are, in our view, of particular interest as they have moved away from the standard route of administration of PDCs (i.v.) and are exploring their potential for oral administration. This aspect is also further explored in the next section.

2.6. Polymer-drug conjugates as polymer therapeutics for digestive diseases

The application of PDC for the treatment of diseases affecting the gastro-intestinal tract is a very interesting case of how one of the main weaknesses of this technology has been cleverly turned into an advantage. PDCs are generally designed for i.v. administration. This is not surprising as their size does not, generally, allow significant absorption to take place in the gastro-intestinal tract. This lack of absorption can, however, be exploited, with advantage, for diseases of the digestive system, particularly those affecting the lower part of the gastro-intestinal tract (GIT).

Ulcerative colitis is a major inflammatory disease of the digestive system which is typically treated with corticoids and other NSAIDs [173]. However, an optimum therapeutic efficacy of these drugs cannot be obtained as these drugs are often released and absorbed in the upper digestive tract, which also results into systemic side effects. Different PDCs were prepared with the aim of providing targeted release of the drugs to the colon (Table 2). A conjugate of PAMAM G3 and 5-aminosalicylic acid was developed for this purpose. PAMAM dendrimers were used in the conjugates due to their negligible absorption after oral administration in rats. Azo compounds (PAH or PABA) were used as linkers which could be hydrolysed by azoreductase enzymes in the colon, allowing localised release [168]. *In vitro* release studies demonstrated that PAMAM-PAH-5-aminosalicylic acid and PAMAM-PABA-5-aminosalicylic acid were chemically stable in the gastric homogenate and in buffers at pH 1.2 and 6.8, and were only negligibly (7.2% and 4.5 %, respectively) released in an homogenate of the small intestine. Further release was detected when PAMAM-PAH-5-aminosalicylic acid and PAMAM-PABA-5-aminosalicylic acid were incubated in cecal content for 12 h (38.2% and 23.5 %, respectively). However, the release of 5-aminosalicylic acid from sulfasalazine was faster with 80% release during the first 6 h of incubation. This indicated the ability of the conjugate to selectively deliver the drug to the colon without premature release in the upper GIT. The same strategy was applied for dexamethasone using a mucoadhesive polymer, specifically poly(dimethylamino)ethyl methacrylate (pDEAEMA) [172]. The conjugate offered a localised release of the drug in the intestine and retained the anti-inflammatory activity of the free dexamethasone

With their ability to effectively localise the release of drugs at targeted segments of the intestine, with prolonged therapeutic effects, macromolecular prodrugs have provided opportunities for treating chronic inflammatory diseases of the GIT.

2.7. Polymer-drug conjugates as polymer therapeutics for bone diseases

Osteoporosis is a common skeletal disease that is related to ageing and menopause. The main feature of this chronic metabolic disorder is increased fragility of bones [183]. Bisphosphonates (alendronate) and anabolic agents (prostaglandin E_1) have showed efficacy for treating osteoporosis [184]. Alendronate has been previously used in PDC conjugates, as a targeting moiety for bone metastasis, with promising *in vivo* results [1]. In an extension of this application, PDCs were therefore suggested for the treatment of osteoporosis (Table 2). These studies mainly focused on reducing unwanted cellular interactions and increasing targeting to bone osteoclasts, which mediate bone resorption.

To reduce the gastric mucosal damage induced by the oral administration of alendronate, a PDC was developed for intrapulmonary administration [182*]. *In vivo* studies in rats showed that the conjugate did not cause any significant elevation in total protein and lactate dehydrogenase levels in the bronchoalveolar fluid when compared to the free drug, which

indicated reduced toxicity of the conjugated alendronate. The conjugate was also accompanied with similar therapeutic activity to that of the native drug.

PDCs of alendronate and prostaglandin E_1were also developed using HPMA as a polymeric carrier to provide selective targeting of the bone cells. The design of these systems depended mainly on using a cathepsin K labile linker (GGProNle) and on using targeting moieties: alendronate itself or $_D$-aspartic acid peptide. These studies indicated that the conjugates could liberate the drugs mainly in osteoclasts by the hydrolytic effect of cathepsin K. Moreover, they gave detailed information about the selectivity of the targeting moieties, where the $_D$-aspartic acid peptide was more selective in distinguishing resorption sites, and alendronate showed stronger binding and recognition of formation and resorption sites [177,179].

Finally, it is important to highlight a recent study which is based on the expression of CD44 receptors on the surface of osteoclasts which mediate the endocytosis of HA (which has been previously highlighted in section 2.2), and on the intracellular hydrolysis of HA by hyaluronidase. Therefore, pamidronate was conjugated to low (L) and high (H) MW HA. *In vitro* studies indicated that both conjugates showed high selectivity towards osteoclasts compared to the free pamidronate. However, the L-HA conjugate was more toxic against the cells than the H-HA and the free drug. Interestingly, the L-HA conjugate could localise inside osteoclast like cells, while H-HA conjugate adhered to the cell surface and did not exhibit any cellular uptake over 12 h [174].

Age-related bone diseases bring significant challenges. As the aging population is progressively increasing, successes in this area, could potentially be particularly impactful.

2.8. Polymer-drug conjugates as polymer therapeutics for ocular diseases

A new area for the application of PDCs was explored within eye related problems. The application of macromolecular prodrugs for treating eye related diseases has been studied recently. Interestingly, the intravitreal administration was used to apply these systems with the intention of enhancing drug accumulation within the defected tissues, and prolonging the $t_{1/2}$ of the drug, Table 2.

The ability of dendrimers to accumulate in inflamed tissues was also employed to achieve selective delivery of intravitreally administered fluocinolone acetonide to the activated retinal microglia. The system was developed by conjugating fluocinolone acetonide to PAMAM G4 dendrimers [185*]. *In vivo* distribution studies in a Royal College of Surgeon rat model revealed the localisation of the dendrimers in activated microglia for 30 days after injection. Furthermore, PAMAM-fluocinolone acetonide was significantly more active than the free drug. Interestingly, *in vitro* studies indicated sustained release of fluocinolone acetonide from PAMAM-fluocinolone acetonide for 91 days in PBS pH 7.4.

The rationale for extending the $t_{1/2}$ was applied for EXP3174 (losartan metabolite), a potent angiotensin II receptor type 1 (AT_1R) blocker, which has shown activity for treating neovascularisation-related retinopathy. However, the intravitreal administration of EXP3174 to improve its activity is limited by its short $t_{1/2}$. Therefore, EXP3174 was conjugated to PAMAM G5 or an 8 arm branched PEG to improve its therapeutic activity [186]. Although the binding affinity of PAMAM G5-EXP3174 was 6-fold greater than that of the 8 arm PEG40K-EXP3174, it was 30 times less than that of the free drug. This loss of affinity of 8 arm PEG40K-EXP3174 could be due to the steric hindrance of the polymeric chain and masking the ligand *via* shroud formation around it by PEG. PAMAM G5-EXP3174 exhibited a unique microarchitecture and provided a greater multivalency which enhanced the affinity towards the receptors.

Intravitreal administration of PDCs has opened new possibilities for treating eye related problems. By offering prolonged activity and localised accumulation within the tissues of the retina, they could improve the therapeutic efficacy of the drugs and prevent the need for their frequent administration.

2.9. Polymer-drug conjugates as polymer therapeutics for wound healing and tissue regeneration

Special consideration has been given recently to applying the concept of polymeric carriers to wound-related problems and tissue regeneration. Within these areas, the main reason for employing PDCs was to increase the water solubility and the stability of the conjugated drugs and to apply the combination therapy (Table 2).

In a very recent study concerning the application of PDCs for enhancing the recovery of spinal cord injury (SCI) [188*], curcumin, a natural anti-inflammatory, was conjugated to polyacetal (PA) to improve its poor water solubility and low stability by providing a controlled release of the drug. *In vitro* studies indicated pH-dependent release of curcumin from a PA-curcumin conjugate, with the release increasing at lower pH. *In vivo* studies revealed that a single administration of PA-curcumin induced a significant increase in motor activity after SCI compared to controls or PA. This was associated with reduced volume of cavitation. Furthermore, PA-curcumin reduced astrogliosis (glial scar formation) and increased the number of neurons fibres. Importantly, PA-curcumin treatment provided a neuroprotective effect accompanied by reduced levels of apoptosis and inflammation. The combined therapy of PA-curcumin and epSCi improved the function recovery from chronic SCI, where they significantly improved the BBB scores, increased the presence of neurons, and reduced the scar area.

Similarly to what noted for bone diseases, wound healing and tissue regenerations issues are expanding, meaning that improvements in these areas could be particularly impactful.

3. Conclusions: perspectives towards the applications of polymer-drug conjugates in diseases other than cancer.

First generation polymer-drug conjugates contained standard cytotoxic agents such as doxorubicin and paclitaxel. Recent development in PDCs for cancer saw the emergence of PDCs which contained more modern agents acting on specific molecular targets (e.g. kinases) and/or used the polymer as a platform to co-deliver two drugs [191]. In all cases, the system was applied to cancer therapy and the key rationale was essentially targeting the tumour tissue, in order to retain efficacy whilst decreasing toxicity.

Application of the concept of PDCs to diseases other than cancer has opened a new research space in this field. As the various therapeutic applications rely on different rationales, it is important to appreciate that with different rationales come different design requirements. While all features of polymer-drug conjugates (polymer, drug, linker, and, if present, targeting group) are important for the overall therapeutic performance, certain features are likely to be more meaningful for diseases than for others. The key design considerations of PDCs for each application depend primarily on the biological barriers that the conjugate needs to cross to reach the site of action, and on its specific therapeutic target. In Table 3, we have therefore summarised the various biological barriers encountered by PDCs within these new therapeutic areas and have highlighted which structural feature, in our view, is particularly key for successful design for a specific disease. Furthermore, the different therapeutic applications are associated with different molecular targets, and as such the "journey" of polymer-drug conjugates from the administration site to the final target might be

different for each application. These new applications have extended the administration routes available to PDCs. While all the traditional PDCs were designed for i.v. administration, Movantik® is on the market for oral administration, and some of the PDC studies summarised here have been proposed for other routes (e.g. intraocular, see Table 2). Each administration route exposes the PDCs to completely different physiological environments. For instance, a PDC administered orally will be exposed to completely different biological barriers than one administered i.v. (stomach: low pH presence of enzymes; blood: neutral pH and a different pool of enzymes) (Table 3). Therefore, again, it is important to consider these needs for each specific case.

Herein, we have identified similarities and differences for the design of PDCs for anticancer and non-cancer applications. There are some general features for the design of PDCs that are important for cancer applications as well as for other diseases. However, applying the concept of PDCs for a specific disease often requires consideration of specific requirements that should be considered on a disease-by-disease basis. Common properties that the polymeric carriers should generally have in all applications are biocompatibility, biodegradababability, safety, and good drug loading capacity. The water solubility and molecular size of the polymer are other key features for the design of PDCs for cancer, in order to enhance the solubility of the chemotherapeutic drug (which are usually hydrophobic in nature) and to control the elimination of the conjugate (if the polymer is not biodegradable) [192]. Some of these properties have received additional interest when selecting a polymer for use in a PDC for diseases other than cancers. For example, the biological degradability and the MW of the polymer are important when the aim is to localise the effect of the conjugated drug at the site of administration. In other cases, polymers are selected that synergise the therapeutic activity of the conjugated drug. Moreover, the tropism of some polymeric platforms towards specific cells, tissues or organs is also considered in order to achieve specific delivery of the conjugate to the desired site, Tables 2 and 3.

The second crucial consideration for the design of PDCs is the drug itself. To develop an effective conjugate for any therapeutic area, the drug should contain a functional group that allow its conjugation and subsequent release at the site of action. Moreover, the drug should be stable at the target site against the environmental conditions (e.g. the low pH and the lysosomal enzymes if the therapeutic target is an intracellular organelle). Finally, the activity of the drug should not be compromised after its release [193*]. For PDCs that are not administered systemically, as summarised in Tables 2 and 3, the drug should be stable in the biological fluids until it reaches the site of action (e.g.: the synovial fluid, the aqueous fluid of the eye).

The third important component of PDC design is the linker. Generally, there are two main properties that the linker should exhibit in order to achieve the required therapeutic effect regardless of its application. First, the linker should be stable until the PDC reaches the intended site of action (blood stream, extracellular fluids, etc.). In addition, the linker should be selectively degraded (chemically or enzymatically) at the intended site to provide a targeted delivery of the drug [194]. In some new therapeutic applications, however, degradability of the linker is not always required, for example when the aim is to prevent the premature release of the drug, or to localise its effects at the intended site by reducing its diffusion through the biological membranes or tissues (Tables 2 and 3).

Finally, the addition of a targeting ligand to the structure of a PDC is not always necessary when developing traditional PDCs for treating cancers. This is because these polymeric systems largely rely on the EPR effect to achieve passive targeted accumulation within tumour tissues compared to the normal tissues which do not show this phenomenon. However, some of the applications described in this review, rely on a targeting moiety to direct the system towards specific cells and tissues, which, in turn, could potentially

maximise the therapeutic efficacy and reduces associated side effects [195,196]. The application of PDCs to diseases other than cancers is providing an increase pool of possible targeting moieties to provide active targeting, especially in pathologies in which passive targeting (EPR or EPR-like) would not occur (Tables 2 and 3).

In addition to the previously mentioned factors, the importance of additional challenges, such as manufacturing (e.g. scaling up, sterilisation requirements, stability issues) and differences in patient populations (e.g. expression of a specific target molecule etc.) are evident in all of the applications and need careful consideration.

In this commentary, we have illustrated the breadth of research currently being undertaken in the field of PDCs. We have analysed each therapeutic area, and the promising results that are emerging, with particular attention on the rationale for using PDCs in these new applications and the key considerations for the design of these systems. PDCs are intrinsically rather complex systems and, in our view, more PDCs can successfully reach the market place only if the complexity of the design of these systems is correctly addressed, and specific needs for each therapeutic application are fully appreciated.

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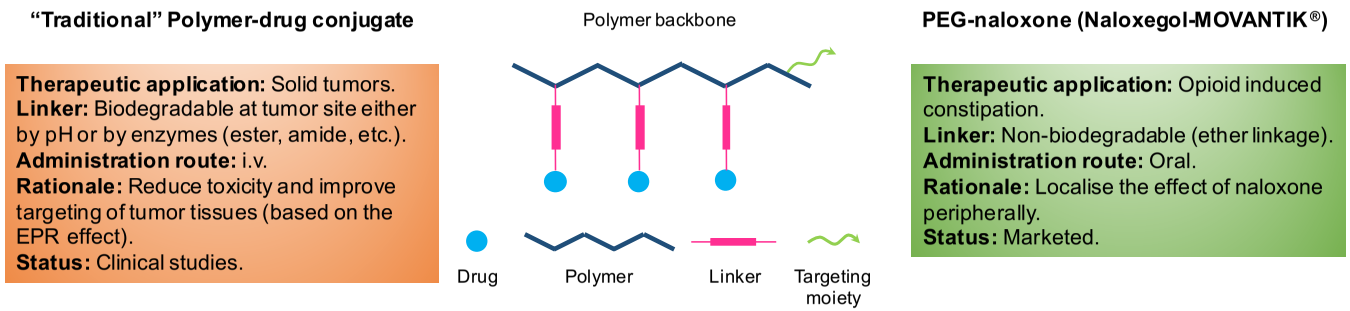


Figure 1. Schematic diagram of PDCs and key differences between traditional PDCs for cancer and the PDC on the market.

Table 1. Rationales for applying PDCs to non-cancer diseases and the mechanisms.

Rationale	**Mechanism**
R1: Controlled/sustained release (with respect to time)	a) pH-dependent release b) Enzyme-dependent release
R2: Increase water solubility	Linking to a water-soluble polymer
R3: Enhance targeting/ controlled release (with respect to space)	a) Receptor-mediated activation b) Tissue affinity/tropism c) pH/GSH/ROS mediated activation d) Enzyme-mediated activation e) Specific feature of vasculature ("EPR-like effect")
R4: Enhance stability and prolong $t_{1/2}$	a) Reduce renal filtration b) Reduce chemical or enzymatic degradation c) Prevent photosensitivity
R5: Combination therapy	a) Polymer and drug have therapeutic effects b) Loading of two drugs
R6: Localized effect	Prevent BBB penetration or keep at the site of administration

Table 2. PDCs for treating non-cancerous diseases.

Rationale of PDCs[a]	PDCs	Biodegradability and type of linker[b]	Targeting ligand	Indications	ROA[c]	Ref
Infection: a) Antibiotics						
Model drug	PEG-PAMAM (G2.5)-penicillin V PEG-PAMAM (G3)-penicillin V	D/E (amide, ester)	N/A[d]	Bacterial	N/A	[11]
R1a	Poly-α,β aspartic acid-isoniazid	N/A (amide)	N/A	Tuberculosis	N/A	[12]
R1a	Poly(DL-succinimide)-isoniazid	D/H (amide)	N/A	Tuberculosis	p.o	[13]
R1a	Low MW PEG-isoniazid	D (amine)	N/A	Tuberculosis	i.v	[14]
R1a, R2	PGA-peptoid 7 PEG-peptoid 7	D/E, H (amide: GG, 4G) (ester: Lact2G, Lact4G)	N/A	Septicaemia	i.p	[15]
R2	Dextran-polymyxin B	N/A (carbamate)	N/A	Septicaemia	i.p	[16]
R3a	Dextran-norfloxacin	D/E (amide: GFAL/GFGG, aminal)	Mannose	Tuberculosis	i.v/i.p	[17,18]
R3a	Carboxymethylglucan-moxifloxacin	N/A (dansyl)	Carboxymethyl	Tuberculosis	i.v	[19]
R3a	PAMAM (G3)-LED 209	N/A (amide)	LED 209	Bacterial	N/A	[20]
R3b	PAMAM (G4)-azithromycin	D/H (ester)	N/A	Bacterial	N/A	[21]
R3b	PAMAM (G4)-erythromycin*	D/H (ester)	N/A	Bacterial	N/A	[22*]
R4a	PEG-vancomycin	N/A (amide)	N/A	Bacterial	i.v	[23]
R4a	PEG-vancomycin	D (amide, carbamate)	N/A	Bacterial	i.v	[24]
Infection: b) Antifungal						
R2	Arabinogalactan-amphotericin B	D/H (amine, imine)	N/A	Fungal	i.v	[35]
R2	mPEG-amphotericin B	D/E (carbamate)	N/A	Fungal	N/A	[36]
R2	Arabinogalactan-amphotericin B	D/H (amine, imine)	N/A	Fungal	i.v	[37]
R2	PEG-amphotericin B	D/E (carbamate, carbonate)	N/A	Fungal	i.v	[38]
R2	Arabinogalactan-amphotericin B	D/H (amine)	N/A	Fungal	i.v	[39]
R3c	PEG-*b*-poly($_L$-lysine)-amphotericin B	D/H (imine)	N/A	Fungal	N/A	[40]
R3c	PEG-amphotericin B	D/H (imine)	N/A		i.v	[41]
R3d	sPEG-amphotericin B	D/E (phenyl-β-D-glucopyranoside)	N/A	Fungal	N/A	[42]
R3d	sPEG-nystatin	D/E (phenyl-β-D-glucopyranoside)	N/A	Fungal	i.v	[43*]
Infection: c) Antiviral						
R1a	mPEG-zidovudine	D/H (ester)	N/A	HIV	p.o	[50]
R1a	mPEG-PCL-acyclovir Chitosan-PCL-acyclovir	D/H (ester)	N/A	HSV-1/2	N/A	[51]
R1a, R2	PHEA-acyclovir	D/H (ester)	N/A	HSV-1/2	p.o/ i.v	[52]
R1a, R2	Sulfonated Chitosan-stavudine	D/H (ester)	N/A	HIV	p.o	[53]
R1a, R4b	Chitosan-stavudine	D/H (phosphoramidate)	N/A	HIV	N/A	[54,55]
R1a, R5a	κ-carrageenan-zidovudine	D/H ester	N/A	HIV	N/A	[56]

R1b	β-cyclodextrin-acyclovir	D/E (ester)	N/A	HSV-1/2	N/A	[57]
R1b	Poly(HEMA)-zidovudine	D/E (ester)	N/A	HIV	p.o	[58]
R1b, R2	PEG-acyclovir	D/E (ester)	N/A	HSV-1/2	N/A	[59]
R1b, R2	PEG-valacyclovir	D/E (amine)	N/A	HSV-1/2	N/A	[59]
R1b, R2	PEG-acyclovir	D/E (Amide: GL)	N/A	HSV-1/2	p.o	[60]
R2, R4a	PHEA-zidovudine	D/E (ester)	N/A	HIV	p.o	[61]
R2, R4a	Dextrin-zidovudine	D/E, H (ester)	N/A	HIV	i.v	[62]
R3a	PEG-saquinavir	D/H (ester)	Biotin/R.I.CK-Tat 9 peptide	HIV	N/A	[63,64]
R3a	Chitosan -lamivudine	D/H (O-P)	Lactobionic acid	HBV	N/A	[65]
R3a, R6	Poly-$_L$-lysine-ribavirin	D/H (phosphate)	Latcosamine	HCV	i.m	[66]
R3b	Dextran (25kDa)-lamivudine	D/H (Ester)	N/A	HBV	i.v	[67]
R4a	Chitosan-stavudine	D/H (ester)	N/A	HIV	N/A	[68]
R4a	mPEG-zidovudine	D/E (ester)	N/A	HIV	p.o	[69]
R4a, R5a	Sulfated laminaripentose-zidovudine	D/H (ester)	N/A	HIV	N/A	[70]
R6	PAA-ribavirin	D/H (ester)	N/A	HCV/HIV	N/A	[71*]
R6	PAA-ribavirin, PMAA-ribavirin	D/H (ester)	N/A	HCV/HIV	N/A	[72]
R6	PVP, PHPMA, PAA, PMAA/ribavirin	-	N/A	HCV/HIV	N/A	[73]
R6	PAA-ribavirin PMAA-ribavirin	D/H (ester)	N/A	HCV/HIV	N/A	[74]
Infection: 3) Antiprotozoal						
Model drug	Dextran-metronidazole	D/H (ester)	N/A	Amoebic dysentery	N/A	[78]
R1a, R2	Arabinogalactan-amphotericin B	D/H (amine, imine)	N/A	Leishmaniasis	s.c/i.v	[79]
R1a, R2	Arabinogalactan-amphotericin B	D/H (amine)	N/A	Leishmaniasis	i.v	[39]
R1a, R4b	PHEA-primaquine, PHPA-primaquine	D/H (carbamate)	N/A	Malaria	p.o	[80]
R3a	HPMA copolymer-NPC1161	D/E (amide: GFLG)	*N*-acetyl mannosamine	Leishmaniasis	i.v	[81,82]
R3a	(HPMA-Amphotericin B) copolymer	D/E (amide: GFLG)	Mannosamine	Leishmaniasis	i.v	[83]
R5b	Poly(HPMA)-amphotericin B-alendronic acid	D/E (amide: GFLG)	N/A	Leishmaniasis	i.v	[84]
R5b	Polyphosphazenes-primaquine-dihydroartemisinin	D/H (O-P and/or N-P)	N/A	Malaria	N/A	[85]
Inflammation and immune system						
Model drug	PHEA-aspirin	D/H (ester)	N/A	Inflammation	N/A	[95]
Model drug	Dextran-naproxen	D/E, H (ester)	N/A	Inflammation	i.artic/p.o	[96,97]
R1a	PHEA-naproxen	D/H (ester)	N/A	Inflammation	p.o	[98]
R1a,b	Poly (HEMA)-diclofenac	D/E, H (ester)	N/A	Inflammation	p.o	[99]

R1a,b	mPEG-ibuprofen PAMAM G4-ibuprofen	D/E, H (ester, amide, peptide)	N/A	Inflammation	N/A	[100]
R1a, R2	Vinyl ether polymer-ibuprofen/ ketoprofen/ naproxen	D/H (amide)	N/A	Inflammation	N/A	[101]
R1a, R5a	Chondroitin sulfate-ibuprofen/ ketoprofen/ naproxen	D/H (ester: PEG)	N/A	Inflammation	p.o	[102]
R2	PAMAM (G0)-naproxen	D/E, H (ester)	N/A	Inflammation	p.o	[103]
R2	PAMAM (G0)-naproxen	D/E, H (amide, ester)	N/A	Inflammation	p.o	[104]
R2	mPEG-tacrolimus	D/E (ester)	N/A	Immunosuppression	N/A	[105]
R2, R4b	Alginate-curcumin	D/H (ester)	N/A	Inflammation	N/A	[106]
R2, R4b	Hyaluronic acid-curcumin	D/H (ester)	N/A	Inflammation	N/A	[107]
R2, R4b, R6	(Acryl amide-dapsone) copolymer	N/A (amide)	N/A	Inflammation	N/A	[108*]
R3a	PAMAM (G5)-methotrexate	N/A (ester)	Folic acid	RA	i.v	[109]
R3a	Hyaluronic acid-methotrexate	D/H (ester)	Hyaluronic acid	RA	i.v	[110]
R3a	PAMAM G5-methotrexate	D/E, H (ester)	Folic acid	RA	i.v	[111]
R3a, R3e	LMWHC-prednisolone	N/A (amide)	N/A	Renal inflammation	i.v	[112]
R3a, R5a	Hyaluronic acid-methotrexate	D/E (amide: AsnPhePhe)	Hyaluronic acid	osteoarthritis	i.artic	[113,114]
R3b	PAMAM (G4)-methylprednisolone	D/E, H (ester: Glutaric acid)	N/A	Inflammation	N/A	[115]
R3b	PAMAM (G4)-erythromycin	D/H (ester)	N/A	Periprosthetic inflammation	N/A	[22*]
R3b	Dextran-methylprednisolone	D/E (ester)	N/A	Immunosuppression	i.v	[116,117*]
R3c, R3e	HPMA copolymer-dexamethasone	D/H (hydrazone)	N/A	RA	i.v	[118]
R3c, R3e	HPMA copolymer-dexamethasone	D/H (hydrazone: GG)	N/A	RA	i.v	[119]
R3c	PAMAM (G3.5)-*N*-acetyl cysteine PAMAM (G4)-*N*-acetyl cysteine	D/H (disulphide)	N/A	Neuroinflammation	N/A	[120]
R3c	PAMAM (G3.5)-*N*-acetyl cysteine	D/H (disulphide)	N/A	Neuroinflammation	N/A	[121*]
R3c	PAMAM (G4)-*N*-acetyl cysteine	D/H (disulphide)	N/A	Inflammation	N/A	[122]
R3c	PEG-polyacrylate-naproxen	OR (phenylboronic ester)	Phenylboronic ester	Inflammation	N/A	[123]
R3e	Linear cyclodextrin-methylprednisolone	D/E, H (thioether)	N/A	RA	i.v	[124]
R4a	PHEA-fenoprofen, PAHA-fenoprofen	N/A (ester, amide)	N/A	Inflammation	N/A	[125]
R4a	PHEA-fenoprofen	D/E, H (ester)	N/A	Inflammation	p.o	[126]
R4c	PHEA-diflunisal, PHEA-naproxen, PHEA-ketoprofen	D/E, H (ester)	N/A	Inflammation	N/A	[127]
R5b	PEG-ibuprofen-eugenol	D/E, H (amide, ester)	N/A	Inflammation	p.o	[128]
R6	PEG-ibuprofen	D/E, H (mercaptoethyl)	N/A	Inflammation	t-dermal	[129]
Nervous system diseases						
R2, R4b	PHEA-$_{L}$-dopa	D/H (ester)	N/A	Parkinson's disease	ICMDT	[141]

R2, R4b	PHEA-$_L$-dopa	D/H (ester)	N/A	Parkinson's disease	N/A	[142]
R3c	PGA-doxycycline	D/E, H (amide, ester, amino acid)	N/A	Amyloidotic disease	i.v	[143*]
R4b	PHEA-dopamine, SMA-dopamine	D/H (amide)	N/A	Parkinson's disease	N/A	[144]
R6	PEG-naloxol	Non-biodegradable (ether)	N/A	Opioid-induced constipation	p.o	[145]
R6	PEG-haloperidol	Non-biodegradable (carbamate)	N/A	Wound healing	N/A	[146*]
Cardiovascular diseases						
R1a,b	PHEA-gemfibrozil PHPA-gemfibrozil	D/E, H (ester, amid)	N/A	Dyslipidaemia and atherosclerosis	N/A	[150,151]
R2	SMA copolymer-AHPP	D/H (amide)	N/A	Hypertension	i.v/p.o	[152]
R2	PEG-AHPP	D/H (amide)	N/A	Hypertension	i.v	[153]
R3c, R4c	PGA-Apaf-1	D/E (amide)	N/A	I/R	N/A	[154]
R4b	PHEA-methyl dopa	D/H (ester)	N/A	Hypertension	N/A	[141]
R5a	PEG-butanediol mononitrate	D/H (ester: β-glutamic acid)	N/A	I/R	i.v	[155]
R6	Dextran (2 MDa)-17β-estradiol	N/A (aminocaproic)	N/A	Coronary heart diseases	i.v	[156*]
Endocrine disease						
R2	PAHA-7β-estradiol	N/A (carbamate)	N/A	Estrogen replacement therapy	N/A	[160]
R2	PAHA-17β-estradiol PAHA-17β-estradiol valerate	N/A (ester, carbamate)	N/A	Estrogen replacement therapy	N/A	[161]
R4b, R6	γ-PGA-phloridzin	Non-biodegradable (ω-amino triethylene glycol)	N/A	Diabetes	p.o	[162,163]
R4b, R6	PAMAM (G3)-phloridzin PAMAM (G3)-arbutin	Non-biodegradable (ω-amino triethylene glycol)	N/A	Diabetes	p.o	[164*]
Digestive diseases						
R3d	Dextran-naproxen	D/E, H (ester)	N/A	Colitis	p.o	[165,166]
R3d	Dextran-methylprednisolone	D/E, H (ester)	N/A	Colitis	p.o	[167]
R3d	PAMAM (G3)-5-aminosalicylic acid	D/E, H (azo bonds)	N/A	Ulcerative colitis	p.o	[168]
R3d	Chitosan-5-aminosalicylic acid	D/E (amide)	N/A	Ulcerative colitis	p.o	[169]
R3d	α/β cyclodextrin-naproxen /sulindac/ flurbiprofen	D/E, H (ester)	N/A	Colitis	p.o	[170]
R3d	Dextran-budenoside	D/E (ester)	N/A	Ulcerative colitis	p.o	[171]
R6	pDMAEMA-dexamethasone	D/H (ester)	N/A	Colitis	p.o	[172]
Bone diseases						
R3a	Hyaluronic acid-pamidronate	N/A (dihydrazide)	Hyaluronic acid	Osteoporosis	N/A	[174]
R3b	PHPMA-alendronate	D/E, H (amide)	Alendronate,	Osteoporosis	i.v	[175]

	PEG-alendronate		aspartic acid peptide			
R3b, R3c	PHPMA-$_D$-(Asp)$_8$, PEG-$_D$-(Asp)$_8$ HPMA copolymer-$_D$-aspartic acid peptide	D/E (amide: GG)	$_D$-aspartic acid peptide	Osteoporosis	i.v	[176]
R3b, R3c	HPMA copolymer-alendronate HPMA copolymer-$_D$-(Asp)$_8$	D/E (amide)	Alendronate, aspartic acid peptide	Osteoporosis	i.v	[177]
R3b, R3d	HPMA copolymer-prostaglandin E_1	D/E (amide: GGPNle)	With or without $_D$-aspartic acid peptide	Osteoporosis	N/A / i.v	[178–180]
R3b, R3d	HPMA copolymer-alendronate	D/E (amide: GGPNle)	Alendronate	Osteoporosis	i.v	[181]
R6	PEG-alendronate	N/A (amide)	Alendronate	Osteoporosis	i.pulmon	[182*]
Ocular diseases						
R1a, R3b	PAMAM (G4)-fluocinolone	D/H (ester: glutaric acid)	N/A	Macular degeneration and retinitis pigmentosa	i.vitre	[185*]
R4b	Branched PEG-EXP3174 PAMAM (G5)-EXP3174	N/A (amide)	N/A	Retinal neovascularization	i.vitre	[186]
Wound healing and tissue regeneration						
R2	Chitosan-kartogenin	D/H (amide)	N/A	Osteoarthritis	i.a	[187]
R2, R4b	Polyacetal-curcumin	D/H (ether)	N/A	Traumatic spinal cord injury	i.t	[188*]
R5a	PAMAM (G3.5)-D(+) glucosamine, PAMAM (G3.5)-D(+) glucosamine 6-sulfate	N/A (amide)	N/A	Prevent scar formation	i.p/s-conjunc	[189]
R6	Chitosan-EDTA	N/A (amide)	N/A	Wound dressing	N/A	[190]

[a.] Rationales defined in Table 1.

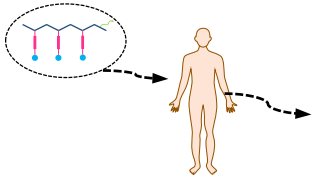
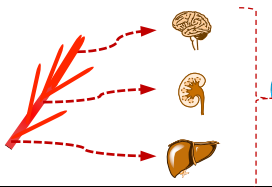
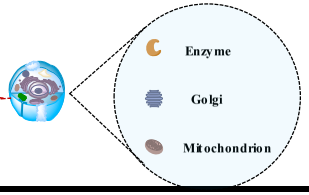
[b.] Biodegradability is defined as degradable (D) or non-biodegradable (ND); Mechanisms of degradability are indicated as enzyme (E) or hydrolysis (H) or redox (redox) or oxidation response (OR).

[c.] Route of administration (ROA); Intracerebral microdialysis technique (ICMDT); Intraarticular (i.artic); Intraperitoneal (i.p); intrapulmonary (i.pulmon); Intrathecal (i.t); Intravenous(i.v); intravitreal: (i.vitre). oral: (p.o); subconjunctival: (s.conjunc); subcutaneous: (s.c); transdermal: (t.dermal).

[d.] Not applicable/not stated (N/A).

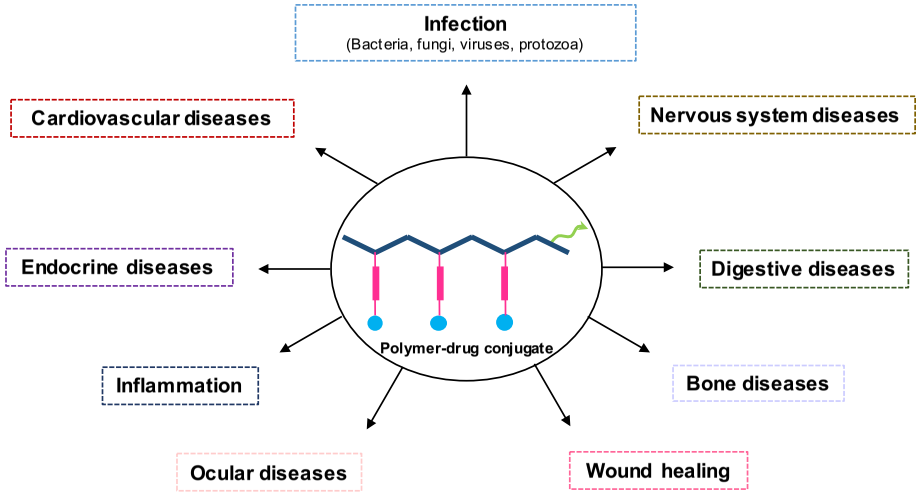
*: The aim of the study was to evaluate erythromycin for the anti-inflammatory effect.

Table 3. A summary of the biological barriers for the application of PDCs for diseases other than cancer and the key considerations for their design.

Biological barriers / Diseases	Step 1: Absorption (From administration site to the blood)	Step 2: Distribution (From the blood to the site of action)	Step 3: Cellular pharmacokinetics (Cellular internalization and trafficking)	Key specific considerations in designing PDCs[a]			
				**Drug** 	**Linker**	**Polymer** 	**Targeting moiety** 
Bacterial infections	GIT pH and enzymes[b]	Blood vessel endothelia to the infected site (except for septicaemia)	Transportation to phagosomal vacuoles and cytoplasm Multidrug resistance	Binding to pathogen cells after release Intracellularly stable	**Enzymatic/pH labile**	**MW of the polymer** **Targetability of the polymeric carrier**	**Receptor recognized moiety**
Fungal infections	N/A	Blood vessel endothelia to the infected site	Transportation to the fungal cell Multidrug resistance	Binding to pathogen membrane after release	**Enzymatic/pH labile**	**Hydrophilicity of the polymer**	-
Viral infections	GIT pH and enzymes[b]	Blood vessel endothelia to the infected site RBCs interaction	Intracellular transportation (cell membrane penetration)	Intracellularly stable	**Enzymatic/pH labile**	**MW of the polymer**	**Receptor recognized moiety**
Protozoal infections	GIT pH and enzymes[b]	Blood vessel endothelia to the infected site	Intracellular transportation to the site of protozoa	Intracellularly stable	**Enzymatic/pH labile**	MW of the polymer **Hydrophilicity of the polymer**	**Receptor recognized moiety**
Inflammation	GIT pH and enzymes[b]	Blood vessel endothelia to the inflamed tissues Tissue pH and enzymes	Reaching macrophages and synoviocytes	Stable in GIT Intracellularly stable	**Enzymatic/pH/GSH/ ROS labile**	**MW of the polymer** **Targetability of the polymeric carrier**	**Receptor recognized moiety**
Nervous system diseases	GIT pH and enzymes[b]	The BBB	Intracellular transportation	Intracellularly stable **Retain activity while conjugated**	Enzymatic/pH labile **Enzymatic/pH stable**	**MW of the polymer**	-
Cardiovascular diseases	GIT pH and enzymes[b]	Blood vessel endothelia	N/A	Stable in GIT Binding to specific receptors after release	**Enzymatic/pH labile**	**MW of the polymer**	-

Endocrine diseases	GIT pH and enzymes[b]	N/A	N/A	**Stable in GIT** **Retain activity while conjugated**	Enzymatic/pH labile **Enzymatic/pH stable**	**MW of the polymer**	**-**
Digestive diseases	GIT pH and enzymes[b]	N/A	N/A	**Stable in GIT**	**Enzymatic/pH labile**	**MW of the polymer**	-
Bone diseases	N/A	Blood vessel endothelia to the bone (resorption lacuna)	Transcytosis	**Stable in extracellular matrix**	**Enzymatic/pH labile**	MW of the polymer **Targetability of the polymeric carrier**	**Receptor recognized moiety**
Ocular diseases	N/A	N/A	Cell membrane penetration	Intracellularly stable	**pH labile**	**MW of the polymer**	-
Wound healing	N/A	Blood vessel endothelia to injury site	Cell membrane penetration	**Stable at injury site** **Intracellularly stable**	**pH labile**	**Hydrophilicity of the polymer**	-

[a]: Bold font indicates the key part of the design of PDCs for a specific rationale.
[b]: In some of studies for each application, the PDCs were evaluated as oral drug delivery systems.
NA: Not applicable.



Graphical abstract. New therapeutic areas for applying the concept of polymer-drug.